ANTI-INFLAMMATORY ACTIVITIES OF PHENOLIC COMPOUNDS IN FRACTIONATED PYROLIGNEOUS ACID FROM SLOW PYROLYSIS OF PALM KERNEL SHELL

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In memory of my loving Father, Late Alhaji Rabi'u Salisu Tahir.

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ABSTRACT

The significant growth in the oil palm industry in recent years in South-East Asia and particularly Malaysia, has subsequently led to the generation of a tremendous amount of oil palm biomass waste. Palm kernel shell (PKS), constitutes a major fraction of this waste and if not properly managed can result in pollution of the environment. PKS has the potential to be thermochemically converted into bio-char, gaseous products and liquids known as pyroligneous acid (PA). PA has been found to contain phenolic compounds and their derivatives, which various studies have shown to have antioxidant and anti-inflammatory effects. There were two main objectives of this research work. First, to determine a viable method of extracting phenolic compounds in sufficiently high concentrations. Second, to investigate a pharmacological mechanism of action through the cyclo-oxygenase (COX) and lipo-oxygenase (LOX) pathway of phenolic compounds produced from PA-PKS. A total of 40.44% of PA was obtained from the pyrolysis of PKS as optimum condition. Extraction of PA using ethyl acetate (CEPA) resulted in 112 fractions which were ultimately pooled into 23 sub-fractions based on thin layer chromatography (TLC) and similarity in the antioxidant activities. Gas chromatography-mass spectrometry (GC-MS) analysis of the CEPA fraction having highest antioxidant activities showed much higher concentrations of phenolic compounds and its derivatives (around 20%) compared to phenol concentration in industrial PA. Further analysis of the CEPA sub-fractions also ascertained the mechanism of action of phenolic compounds and their derivatives. Determination on the pharmacological activity for CEPA resulted in IC_{50} values of 17.04 % for the COX assay and 5.25 % for LOX, which was higher than IC_{50} for aspirin (control experiment) with values of 19.70 % (COX) and 40.35 % (LOX) respectively. The Malondi-aldehyde assay indicate high efficiency of CEPA as lipid peroxidation agent. From the pyrolysis work, phenol concentration was shown to increase with dual inhibition of the COX and LOX pathways. As a conclusion, PKS was demonstrated to have the potential to be used as one of the raw materials for the production of highly valuable compounds.

ABSTRAK

Pertumbuhan pesat industri kelapa sawit di Asia Tenggara dan terutamanya di Malaysia, telah menghasilkan banyak sisa biojisim kelapa sawit. Salah satu dari sisa biojisim kelapa sawit yang banyak dihasilkan ialah sisa isirung sawit (PKS) dan jika tidak diuruskan dengan mampan boleh mengakibatkan kesan pencemaran kepada alam sekitar. PKS berpotensi untuk diubah secara proses termokimia ke bio-char, produk gas dan komponen cecair yang dikenali sebagai asid piroligneous (PA). Kandungan fenolik dan terbitannya yang terdapat dalam PA berpotensi untuk digunakan dalam berbagai kajian seperti agen anti-pengoksidaan dan anti-radang. Terdapat dua objektif utama dalam kerja penyelidikan ini. Objektif pertama adalah untuk menentukan kaedah yang paling berkesan untuk mengekstrak sebatian fenolik dalam kepekatan yang cukup tinggi. Kedua adalah untuk menyiasat mekanisme tindakan farmakologi melalui laluan cyclo-oxygenase (COX) mahupun lipo-oxygenase (LOX) sebatian fenolik yang dihasilkan dari PA-PKS. Sebanyak 40.44% PA berjaya diperoleh melalui proses pirolisis PKS pada keadaan optimum. Pengekstrakan PA menggunakan etil-asetat (CEPA) menghasilkan 112 pecahan yang akhirnya dikumpulkan kepada 23 sub-pecahan berdasarkan teknik kromatografi lapisan nipis (TLC) dan persamaan profil aktiviti antioksidan. Analisis spektrometri kromatografi gas (GC-MS) bagi pecahan CEPA yang menunjukkan aktiviti antioksidan paling tinggi menunjukkan kepekatan sebatian fenolik dan terbitannya yang lebih tinggi (sekitar 20%) berbanding kepekatan fenol yang terdapat dalam PA yang dihasilkan oleh industri. Analisis lanjutan bagi sub-pecahan CEPA turut menyokong mekanisme tindakan sebatian fenolik dan terbitannya. Penilaian terhadap aktiviti farmakologi CEPA pula memberikan nilai IC_{50} 17.04 % bagi ujian COX dan 5.25 % bagi ujian LOX, yang merupakan nilai yang lebih tinggi berbanding nilai IC_{50} aspirin (ujikaji kawalan) masing-masing dengan nilai 19.70 % (COX) dan 40.35 % (LOX). Hasil ujikaji Malondi-aldehid pula menunjukkan kecekapan CEPA sebagai perencat peroksidasi lipid yang tinggi. Hasil yang diperolehi dari pirolisis menunjukkan penambahan kepekatan fenol dengan tindakan dual-perencatan melalui laluan COX dan LOX. Sebagai kesimpulan, PKS berpotensi untuk digunakan sebagai salah satu sumber bahan mentah untuk penghasilan sebatian yang mempunyai nilai tinggi.

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LIST OF ABBREVIATIONS

AA	-	Arachidonic Acid
AIL	-	Acid Insoluble Lignin
AA	-	Arachidonic Acid
ABTS	-	2,2′-Azinobis (3-Ethyl-Benzo-Thiazoline-6-Sulphonic)
ASL	-	Acid Insoluble Lignin
ASTM	-	American Society for Testing and Materials
BHT	-	Butylated Hydroxyl Anisole
$CaCO_3$	-	Calcium Carbonate
CEPA	-	Concentrated Ethyl-Acetate Pyroligneous Acid
CC	-	Column Chromatography
C.I.O.M.S	-	Council for International Organization of Medical Sciences
$CHCl_3$	-	Chloroform
COX	-	Cyclooxygenase
DPPH	-	2, 2-Di-Phenyl-1-Picryl-Hydrazyl
DTG	-	Derivative Thermogravimetric
EFB	-	Empty Fruit Bunch
EtOAc	-	Ethyl Acetate
EPA	-	Ethyl-Acetate Pyroligneous Acid
$FeCl_3.6H_20$	-	Ferric Chloride
$FeSO_4$	-	Iron (II) Sulphate
FPA	-	Filtered Pyroligneous Acid
FFA	-	Free Fatty Acid
FRAP	-	Ferric Reducing Antioxidant Power
FTIRS	-	Fourier Transform Infrared Spectroscopy
GAE	-	Gallic Acid Equivalent
GCMS	-	Gas Column- Mass spectrophotometry
H	-	Hydrogen
HEX	-	Hexane
HCl	-	Hydrochloric Acid
H_2SO_4	-	Sulphuric Acid

IPA	-	Industrial Pyroligneous Acid
IL	-	Interleukins
LT	-	Leukotrienes
LX	-	Lipoxins
Me	-	Methanol/Meth
MDA	-	Malondialdehyde
MF	-	Mesocarp Fibre
MPOB	-	Malaysia Palm Oil Board
NMR	-	Nuclear Magnetic Resonance
N_2	-	Nitrogen
Na_2CO_3	-	Sodium Carbonate
NDGA	-	Nordihydroguaiaretic Acid
NSAID	-	Non-Steroidal Anti-inflammatory Drug
NIST	-	National Institute Standard and Technology
O	-	Oxygen
OPF	-	Oil Palm Frond
OPT	-	Oil palm Trunks
PA	-	Pyroligneous Acid
PG	-	Prostaglandins
POME	-	Palm Oil Mill Effluents
PUFAs	-	Polyunsaturated Fatty acids
PK	-	Palm Kernel
PKS	-	Palm Kernel Shell
ROS	-	Reactive Oxygen Species
RPA	-	Refined Pyroligneous Acid
RT	-	Residence Time
rpm	-	Revolutions Per Minutes
S	-	Sulphur
SAID	-	Steroidal Anti-Inflammatory Drug
SD	-	Standard Deviation
SEM	-	Standard Error of Mean
STD	-	Standard
TBARS-	-	Thio-barbituric Acid Reactive specie

TEAC	-	Trolox Equivalent Antioxidant Capacity
TLC	-	Thin Layer Chromatography
TG	-	Thermogravimetric
TGA	-	Thermogravimetric Analysis
TPC	-	Total Phenolic Content
TPTZ	-	Tri-pyridyltriazine
TNF	-	Tumour Necrosis Factor
UV	-	Ultra Violet Spectroscopy

LIST OF SYMBOLS

%	-	Percentage
cm	-	Centimetre
g	-	Gram
ha	-	Hectare
℃	-	Degree Celsius
µg	-	Microgram
µl	-	Microliter
IC_{50}	-	Half Maximal Inhibition Concentration
Hr	-	Hour
K	-	Kelvin
Kg	-	Kilogram
L	-	Litre
M	-	Molar
Min	-	Minute
mg	-	Milligram
mL	-	Millilitre
Mm	-	Millimetre
Mmol	-	Millimole
mwt.	-	Molecular Weight
Nm	-	Nanometre
rpm	-	Ramp Per Minute
S	-	Seconds
wt.	-	Weight
μg	-	Microgram
µL	-	Microliter
µM	-	Micromolar

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CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Palm oil is a major economic crop in countries like Colombia, Indonesia, Malaysia, Nigeria and Thailand (Lam and Lee, 2011). Malaysia is the second largest producer of oil palm in the world where around 5.74 million hectares of land cultivated for oil palm plantation with an estimated production of 19.3 million tonnes palm oil and 1.93 million tonnes of palm kernel oil (MPOC, 2017). Palm oil processing leads to the generation of huge amounts of lignocellulosic biomass such as empty fruit bunch (EFB), palm kernel shell (PKS), oil palm frond (OPF), mesocarp fibres (MF), oil palm trunk (OPT) and palm oil mill effluent, POME (Board, 2011). For crucial survival of the oil palm industry and their associated economic benefits to the producing countries, there is a need for sustainable utilization of the biomass waste without any harmful effect to the environment. In general, biomass are considered as highly potential to become a sustainable and bio-renewable resources for the production of energy and valuable fine chemicals which can ultimately reduced the dependency on diminishing supply of fossil-based fuels (Núñez-Regueira et al, 2001; Isikgor and Becer, 2015). Biomass are produced from the photosynthetic activity of plant that resulted in the production of hemicellulose, cellulose and lignin. It is considered as carbon neutral releasing naturally occurring carbon, by recycling the used carbon replenished with production from planted trees. Sustainable utilization of biomass results in waste reduction and also contributes to the overall reduction of CO_2 in the atmosphere thereby limiting the effects of green-house gases (Omer, 2012).

Various oil palm biomass management techniques are available such as formulation into animal feed (EFB, OPF), biochemical treatment to produce five-carbon based sugars (OPF, OPT), thermal processing in the production of bio-oil and bio-char (PKS) and as additional materials in the production of bio-fertilizer (POME).

Thermal conversion technique such as pyrolysis offers a simple, highly reproducible, cost effective and eco-friendly process (Kim, 2015). Biomass can be converted into solid, liquid and gas products in the presence of an inert gas, through the process of pyrolysis (Collard and Blin, 2014). The yield and type of products is dependent on the heating conditions and parameters (Zanzi Vigouroux et al, 2004; Demirbas and Arin, 2002; Bridgwater et al, 2007; Demirbaş, 2001). Pyrolysis can be categorised into three distinguished processes; slow, fast and flash pyrolysis based on their heating parameters, with fast and flash pyrolysis occurring at temp ≥500 °C and characterised with high liquid and gaseous yield respectively. Fast pyrolysis is characterised with high liquid production at high temperatures , high heating rate and shorter residence times while flash pyrolysis is characterised with rapid reaction time occurring for a few seconds or even less and high heating rate (Goyal et al, 2008; Akhtar and Amin, 2012).While slow pyrolysis is characterised with high char production occurring at temperature condition ≤ 400 °C. The slow decomposition of biomass over a wide temperature allows for formation of different chemical compounds (Akhtar and Amin, 2012). The liquid product of pyrolysis i.e. pyroligneous acid which has been shown in several studies to exhibit antioxidant and free radical scavenging activities (Loo et al, 2007; Ma et al, 2014).

Antioxidants are molecules or compounds that protect the body's cells against free radicals. Antioxidants supress the activity of free radicals produced in our body resulting from different biological functions by counteracting them before they can lead to oxidative damage (Pourmorad et al, 2006). Antioxidants are molecules or compounds that protect the body's cells against free radicals. Antioxidants supress the activity of free radicals produced in our body resulting from different biological functions by counteracting them before they can lead to oxidative damage (Pourmorad et al, 2006). The oxidative degradation of lipids "lipid peroxidation" is the results of free radical activity from oxidative cell death. Membrane lipids containing polyunsaturated fatty acids are the major targets, due to their carbon- carbon double bonds which have reactive hydrogen groups (Ayala et al, 2014). The membrane lipids loose electrons to free radicals which results in the production of lipid- peroxyl radicals (endoperoxides and hydro peroxides) which induce oxidative stress. The peroxyl radicals are reactive oxygen species (ROS) responsible for oxidative cell damage and also have the ability to initiate degenerative processes such as inflammation in the body system (Wang et al., 2002). Oxidative stress induced by the activity of these ROS is reduced or prevented by the body natural defence system. The body also has the ability to utilize antioxidants to terminate the activities of these free radical reactive oxygen species (Zhang et al, 2011). The measure of lipid peroxidation occurring in the body can be measured as a quantity of level of lipid hydro-peroxides in the body. One of the end products of hydro-peroxides is malondi-aldehyde (Buege and Aust 1978). Malondialdehyde (MDA) a naturally occurring product, which acts as a convenient index and measures the level of oxidative damage resulting from the activities of free radicals (Marnett 1999; Ruberto and Baratta, 2000; Gaschler and Stockwell, 2017).

The ability to delay or inhibit the free radicals is referred to as the antioxidant ability (Mahdi-Pour et al, 2012) which helps in preventing degenerative diseases resulting from oxidative damage. Antioxidants thus have beneficial roles in the human body (Yu et al, 2008). The occurrence of antioxidant and free radical scavenging compounds in plant biomass can be indicated from the presence of phenolic compounds. Phenolic compounds occur naturally in plants and are hydroxyl derivatives of carboxylic acids which are derived from either the benzoic or the cinnamic acid group. Phenolic compounds include phenolic acids, flavonoids and tannins and vary depending on the number and position of the hydroxyl and also on the methoxylation of their aromatic rings. Benzoic acid derivatives of phenolic compounds include gallic, proto-catechuic, p-hydroxy benzoic and vanillic acid, while caffeic, p-coumaric and ferulic acids are derivatives of cinnamic acid (Bu et al, 2012; Brebu and Vasile, 2010; Neutelings, 2011; Isikgor and Becer, 2015). Studies have indicated the presence of phenolic compounds in most plants including oil palm biomass (Demirbas, 2001; Li et al, 2017).

Due to their antioxidant properties, phenolic compounds are also beneficial in the treatment of inflammatory and associated diseases (Jiang and Dusting, 2003). Inflammation is a complex series of biological responses to external stimuli such as harmful pathogens, irritants and damaged cells (Phanse et al, 2012). This process occurs through various mechanisms resulting in increased blood flow and release of lipid mediators (Martel-Pelletier et al, 2003). The most strongly associated mediators are the prostaglandins (PGs) and the leukotrienes (LTs) which, are products of the cyclooxygenase (COX) and lipoxygenase (LOX) pathways respectively (Vane and Botting, 1987). The prostaglandins products of the COX pathway are a group of hormone-like lipid compounds with a wide variety of strong physiological functions. They are involved in protection of the stomach mucosa, platelets aggregation, kidney function regulation and also associated with pathological functions such as inflammation, fever and pain (Botting, 2006; Díaz - González and Sánchez - Madrid, 2015). The leukotrienes (produced through the LOX pathway) are potent lipid bio-effectors and are particularly important in inflammation. They act as chemotactic and chemotaxis agents, contract airways, stimulate muscular secretions and increase microvascular permeability (Bertolini et al, 2002; O'Donnell, 1999). They also play a vital role in the development of gastrointestinal ulcers (Fiorucci et al. 2001; Bertolini, Ottani, and Sandrini 2002). Inhibition of 5-lipoxygenase indirectly results in reduced expression of cytokine of TNF-alpha that has a major role in inflammation (Bertolini, Ottani, and Sandrini 2002). The inhibition of the COX pathway may also result in shunting of the Arachidonic acid (AA) cascade to the LOX pathway (Martel-Pelletier et al. 2003). The synergistic effect of both the COX-2 and LOX-5 pathways results in inflammatory responses (Martel-Pelletier et al, 2003).

The treatment for inflammation (anti-inflammation) is generally carried out using steroidal (corticosteroids) and non-steroidal (NSAIDs) drugs. NSAIDs act as analgesic, antipyretic and anti-inflammatory drugs and are prescribed as first line of treatments for rheumatic disorders and general inflammation (Fiorucci et al, 2001). However, these drugs are also associated with many adverse effects. Anti-inflammatory drugs used in alleviating symptoms of inflammation bind reversibly/ irreversibly to the active site of the enzyme to inhibit the action of the substrate arachidonic acid (Botting, 2006). They thereby prevent the production of inflammatory mediators. These mediators are not only involved in inflammatory effects but are also responsible for maintaining physiological functions of the body. Thus inhibition of COX and LOX pathways results in reduction of the concurrent curtailed production of the associated side effects of gastro-damaging and broncho-constrictive associated with these enzymes cyclooxygenase and leukotrienes respectively. One effective and less damaging strategy in treating inflammation is the development of dual COX/LOX inhibitors from natural sources. For this to be economically viable, however, a method of extracting phenolic compounds from biomass waste in sufficiently high concentrations must be used. This will simultaneously serve as a method of reducing biomass waste in oil palm producing countries like Malaysia.

1.2 Problem Statement

Over the years, the country's oil palm industry has been pressured to provide solutions to sustainability by managing environmental problems resulting from the generation of waste products produced by the palm oil processing industries. Utilization of oil palm biomass waste in a sustainable and renewable manner is thus a necessary requirement for the oil palm industry. One type of oil palm biomass available which is least studied is the palm kernel shell (PKS). PKS has been thermochemically converted into bio-fuel with the similar yield to that of EFB. However, it has lower viscosity (after centrifugation) and calorific value and also contains a higher water content when compared to EFB (Abnisa et al, 2013). PKS bio-fuel used in electricity generation also has lower energy than that of EFB (Shafie et al, 2012). Nevertheless, PKS has a much higher lignin (~50.7% dry weight) with lower moisture contents (<10 wt %) compared to other oil palm wastes (Goh et al, 2010). It is well known that the degradation of lignin generally leads to the production of phenol, guaiacol, syringol, pyrocatechol and their derivatives, which are mostly found in the liquid fraction of the by-products obtained i.e. pyroligneous acid. Therefore, this study focused on the elucidation on the feasibility of using a specially designed pyrolysis reactor designed by heat temps, Malayasia to produce pyroligneous acid from PKS where the refined fractationated pyroligenous acid is targeted to contain high concentration of phenolic contents with optimum purity. It would then be evaluated for potential anti-oxidant and anti-inflammatory activities.

Due to adverse effects such as gastric toxicity caused by non-steroidal anti-inflammatory drugs (NSAID), the use of these drugs as anti-inflammatory agents have proved to have repercussions (Whitehouse, 2011; Xu et al, 2009; Sostres et al, 2010).

The mechanism of action of these drugs is through the inhibition of the enzymes of the COX and LOX-5 pathways as their use results in three times more toxicity to the gastric mucosa (Jick, 1994). Therefore, there is need for alternative anti-inflammatory drugs with synergistic inhibitory effects without these undesirable side effects. Hence, the use of renewable PKS biomass as a cheap and sustainable green alternative with potent efficacy and possibly without associated side effects of the synthetic drugs. Although, the traditional use of oil palm tree in treating of inflammatory conditions has been prevalent over time, the biologically active components in these extracts that are responsible for the anti-inflammatory properties remain unclear. There is also limited literature related to the use of PKS as raw materials for the extraction of phenol and its derivatives in treating anti-inflammatory diseases. Although previous studies have shown the potential uses of PA in treatment of various diseases. Its increased concentration with application has been associated with increased acidity (Grewal et al, 2018). Recent studies by (De Lima et al, 2019) on eco-toxicological screening using pyroligneous acid produced from eucalypt wood fines showed acute toxicity for planktonic crustacean (D. magna), with minimum toxicity for higher plant (A. cepa). This toxic effect was found to be negative for genotoxicity screening on aquatic species (RTG-2 trout rainbow gonad tissue).

1.3 Research Objectives

The main objectives of this research are as follows:

1. To determine the physio-chemical characteristics of pyroligneous acid produced from slow pyrolysis of palm kernel shell, using standardized parameters.
2. To select high phenolic fractions of pyroligneous acid based on antioxidant and anti-inflammatory activities.
3. To study the mechanism of action of phenolic fractions using dual COX/LOX inhibition and lipid peroxidation using the malondi-aldehyde.

1.4 Research Hypothesis

Pyroligneous acid condensate produced from slow pyrolysis of palm kernel shell contain phenolic compounds and its derivatives which possibly have anti-inflammatory activities which can be applied as a natural based anti-inflammatory agent using dual inhibitors through the COX and LOX pathway responsible for release of inflammatory mediators.

1.5 Scope of Research

The study is focused on the following:

1. Evaluation of the characterized palm kernel shells collected from different sampling points for elemental, proximate and composition analysis to determine the highest lignin content and favourable conditions to enable high yield production of PA.
2. Slow pyrolysis of the characterized palm kernel shell using a specially designed laboratory scale reactor from Heat Temps Engineering, Malaysia with standardized parameters (Final temperature, residence time, Nitrogen Flow and heating rate).
3. Evaluation of the different fractions for total phenolic content (TPC) and antioxidant activity using different assays namely DPPH (2, 2-Diphenyl-1-Picryl-Hydrazyl) and FRAP (Ferric reducing antioxidant power).
4. Seperation of the different bioactive compounds into different fractions from the concentrated ethyl acetate pyroligneous acid produced was carried out using column chromatography.
5. Chemical identification and characterization using Gas Chromatography-Mass Spectrophotometer (GC-MS) for selected fractions with high phenolic and antioxidant activity, with pyroligneous acid obtained from the Malaysian Palm Oil Board (MPOB) as benchmark.

6. Assesment of oxidative stress using malondialdehyde lipid peroxidation assay kit to assess the antioxidant effectiveness of the different fractions with high phenolic and antioxidant activities.
7. Determination of the anti-inflammatory activity in-vitro of the pyroligneous acid fractions using the COX-2 (Human inhibitor screening assay kit) and the LOX (Lipooxygenase Inhibitor Screening Assay Kit) through the COX and LOX metabolic pathway respectively.

1.6 Significance of Study

PKS as a valuable source of lignin which is a rich in bioactive compounds that can provide high value bio-added chemicals. The exploitation of this abundant lignocellulose biomass would provide a cheap and sustainable means of waste management, with possible pharmacological application in the medical field. There are several studies relating the various application of PA produced from various biomass sources as antioxidant, antimicrobial and antifungal agents. However, there are currently very limited literature resources and scientific studies available with regards to the application of PA in anti-inflammatory treatment. This is especially the case for oil palm biomass waste such as PKS. The mechanism of the biologically active phenolic compounds from the PA extract of PKS as an anti-inflammatory agent is thus currently poorly understood. This study addresses this issue by explaining the mechanism of action of PA towards mitigating inflammation through the simultaneous inhibition of the COX and LOX-5 enzymes. Hence, the finding from this study can become the platform for the viable extraction and efficacy of anti-inflammatory studies from oil palm waste biomass

1.7 Thesis Organisation

This thesis is organised into five chapters. Chapter 1 is an introduction including a background of the research, problem statement, and objectives of the research, research scope, research hypothesis and significance of study. The main contributions of the thesis are also listed.

Chapter 2 is a review of existing literature concerned with previous works published on the biomass, oil palm biomass, thermochemical conversion process, pyroligneous acid production and its application, phenolic compounds and their uses. The mechanism of action and the effect of non-steroidal anti-inflammatory drugs. Finally Research gaps are identified based on the review of available literature.

Chapter 3 presents the methodology including the materials and laboratory equipment used in carrying out the research work. The procedure on pyrolysis, separation process, antioxidant analysis, column chromatography, and thin layer chromatography and anti-inflammatory and antioxidant efficiency analysis are outlined.

Chapter 4 presents and discussed the results obtained from the research. Experimental results of the chemical and physiochemical characteristics of the palm kernel samples are first presented. The results of fractionation of the PA-PKS samples, antioxidant and *in vitro* anti-inflammatory analysis and assessment of anti-oxidant efficiency of the different fractions are also presented and compared with existing works in the literature.

Chapter 5 draws a conclusion on the research and gives recommendations of areas of further work regarding the mechanism of action, and bioactive compounds of choice.

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